REMARKS:

Applicants' representatives would like to thank Examiner Bertoglio for the courtesy extended during the telephone interview on October 13, 2010.

The preceding claim amendments and the following remarks are submitted as a full and complete response to the Office Action issued on June 30, 2010. Claims 1 and 6 have been amended to recite "wherein implantation or pregnancy rate of human oocytes after devitrification and *in vitro* fertilization is higher than implantation or pregnancy rate of human oocytes vitrified on a gold grid using liquid nitrogen." Claim 5 has been amended to recite "wherein implantation or pregnancy rate of human oocytes after in vitro fertilization is higher than implantation or pregnancy rate of human oocytes vitrified on a gold grid using liquid nitrogen." New claim 9, which is directed to vitrified human oocytes produced by the method of claim 1, is added. Support for these claim amendments can be found throughout the specification, for example, on pages 7-10 of the specification and Figures 4 and 5. No new matter has been added. Although claim 9 is not directed to a method and thus might be provisionally withdrawn from this application, it is entitled to be rejoined once claim 1 is found allowable since claim 9 depends from claim 1. Upon entry of these claim amendments, claims 1, 3, 5, 6 and 9 are pending in this application.

Interview Summary

During the October 13, 2010 interview, Applicants explained to the examiner the unexpected results of the claimed method based on the original disclosure including

pages 8-10 of the specification, and Figures 4 and 5. The Examiner asked Applicants to amend the claims to recite the unexpected results, and to submit, from the original disclosure, basis for such unexpected results. Applicants agreed to file a Request for Continued Examination with the understanding that the claim amendments made herein may require an additional search and consideration after final rejection.

Response to Rejections Under 35 U.S.C. § 103

The Patent Office has maintained the rejection of claims 1, 3, 5 and 6 under 35 U.S.C. § 103(a) as obvious over Yoon in view of Wheeler and further in view of Martino. The Patent Office appreciates Applicants' argument that given the absence of teaching in Wheeler regarding vitrification of oocytes, one would not have been motivated from Wheeler to use a gold grid in vitrifying oocytes as taught by Yoon since the technologies of the two references are different. However, the Patent Office asserts, among others, that "[o]ne skilled in the art would attempt to find the best freezing rate for a particular species by varying the temperature of the coolant (i.e., liquid vs. slush) as well as the material the grid is made of (i.e. copper vs. gold)" in light of the teachings of Martino discussing the differences between various species of oocytes and the different requirements for freezing rates. With respect to the disclosure of Martino, the Patent Office further alleges that since Martino shows differential success with liquid and slush nitrogen, the art taken as a whole shows that different species are most successfully vitrified using different cooling rates. The Patent Office's position seems to be that since cooling rates can be affected by use of different combinations of liquid/slush nitrogen and different freezing platforms, copper grids/gold grids/straws etc, it is a

matter of routine experimentation and design choice to determine the best combination for various oocytes. According to the Patent Office, "[w]hile the art fails to teach the best combination for use in vitrifying human oocytes as claimed, the claimed combination is merely a combination of familiar elements according to known methods." Applicants respectfully traverse this rejection.

Applicants still maintain the position that due to the failure of Wheeler in teaching vitrification of oocytes, the cited prior art references, even taken as a whole, still fail to teach or suggest all the elements of the claimed method. Moreover, assuming *arguendo* that all elements of the claimed method had been taught by the cited prior art, it is well settled that the claims would not have been obvious if the combination yielded more than predictable results, which is the case in the claimed method. As clarified in the 2010 *KSR* Guidelines Update, in accordance with MPEP §2143 A(3), "a proper rejection based on the rationale that the claimed invention is a combination of prior art elements also includes a finding that results flowing from the combination would have been predictable to a person of ordinary skill in the art. If results would not have been predictable, Office personnel should not enter an obviousness rejection using the combination of prior art elements rationale, and should withdraw such a rejection if it has been made."

As explained below, therefore, Applicants respectfully submit that the claimed method would not have been obvious to one skilled in the art over the cited references, alone or in combination, and thus reconsideration and withdrawal of this obviousness rejection are respectfully requested.

As the Patent Office also has admitted, Yoon does not teach use of a gold grid or use of nitrogen slush. In an effort to cure Yoon's lack of teaching regarding using nitrogen slush in vitrification of human oocytes, the Patent Office has relied on the disclosure of Martino. However, contrary to the Patent Office's position, Martino's teaching rather serves as a strong proof evidencing that the results of the claimed method would not have been predictable.

More specifically, Martino compares the survival, cleavage, and blastocyte development of bovine oocytes vitrified in liquid nitrogen with those vitrified in nitrogen slush (Figure 4). In Martino, this comparison reveals that, in the case of bovine oocytes, vitrification in liquid nitrogen is preferable over vitrification in nitrogen slush (Figure 4 of Martino). However, Martino does not disclose or suggest that the selection of grids and/or cooling rates will have any effect on implantation or pregnancy of bovine oocytes let alone implantation or pregnancy of human oocytes. Rather, Martino goes further to suggest that

> ". . . our previous observations indicate that fertilization itself is not affected by chilling to 0 °C for 1 min or less. . . . the fact that similar development rates were obtained with oocytes cryopreserved on grids and with those only exposed to the CPA also suggests that It is the CPA alone, not the chilling, that was probably responsible for the lower fertilization rates."

Martino, page 1068, left column, lines 6-11.

This statement in Martino suggests that these parameters such as grids and/or chilling rates, are probably not critical for determining fertilization rates.

Therefore, at best, the predictable results flowing from the disclosure of Martino would be that even in implantation or pregnancy rate of oocytes, either in bovine or human, vitrification using nitrogen liquid would be better than that using nitrogen slush.

However, the results produced from the claimed method are contrary to these predictable results, that is, the implantation and pregnancy rates in human when using nitrogen slush are higher than when using liquid nitrogen. Moreover, the difference in these rates between using nitrogen slush and liquid nitrogen is unexpectedly large, especially when compared to the relatively smaller differences between using liquid nitrogen and nitrogen slush for survival, fertilization and cleavage rates. The original disclosure of the present application fully supports this conclusion. *See* pages 8-10, Figures 2 to 5. That is, the details of the comparative studies between using liquid nitrogen and using nitrogen slush in vitrifying human oocytes are well described on pages 8-10 of the specification and the results are demonstrated in Figures 2 to 5. While the predictable results from combining the disclosures of the cited prior art would be the survival rate of human oocytes after vitrification would be better when using liquid nitrogen than when using nitrogen slush, Figures 2 and 4 show the results contrary to the predictable results. That is, both Figures 2 and 4 show higher survival rates of human oocytes after vitrification using nitrogen slush than when using liquid nitrogen, (89.0% v. 82.4% in Fig. 2 and 82.9% v. 68.6% in Fig. 4[1]). This result itself is sufficient to demonstrate the unpredictable results of the claimed method in comparison with the prior art method using liquid nitrogen, especially given the disclosure of Martino showing superior survival results after using liquid nitrogen for vitrification than using nitrogen slush. This unpredictable result of the claimed method is further bolstered by the clinical results reported in Figure 5. Figure 5 shows that according to the presently

[1] Phase I is data from clinical studies using the prior method using liquid nitrogen for vitrifying human oocytes and Phase II is data from clinical studies when using the presently claimed method.

claimed method, it is possible to obtain vitrified human oocytes that produce significantly higher implantation and/or pregnancy rates in humans as compared to the method disclosed in the prior art, *i.e.*, when human oocytes were vitrified in liquid nitrogen. More particularly, as demonstrated in Figure 5, implantation rates (14.2% with nitrogen slush vs. 6.4% with liquid nitrogen) and pregnancy rates (43.3% with nitrogen slush vs. 21.4% with liquid nitrogen) were both increased more than 2-fold when nitrogen slush was used. These results are also illustrated on page 10 of the specification. That is, it is reported that "13 patients achieved clinical pregnancies," "[f]our pregnancies were delivered 5 normal babies...and 7 pregnancies are well ongoing." Thus, the results disclosed in the present specification demonstrate that vitrified human oocytes made and used according to the presently claimed method produce unexpectedly and significantly increased rates of implantation and pregnancy in humans when compared to the human oocytes vitrified in liquid nitrogen. These results are especially unexpected and more than predictable results given the prior art disclosure, that is, (1) liquid nitrogen is better that nitrogen slush in terms of morphological survival, cleavage and blastocyte of vitrified bovine oocytes and (2) fertilization is not affected by chilling rates that regardless of using nitrogen liquid or nitrogen slush.

As such, the claimed method yielded more than predictable results and thus would not have been obvious over the combined disclosure of the cited prior art references. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

In view of the above remarks, Applicants believe that all of the Examiner's rejections set forth in the June 30, 2010 Office Action have been fully overcome and that the present claims fully satisfy the patent statutes. Applicants, therefore, believe that the application is in condition for allowance.

The Director is authorized to charge any fees or overpayment to Deposit Account No. 02-2135.

The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the application.

Respectfully submitted,

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